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CYANIDE IN BREATH AS A MARKER FOR CYANIDE POISONING

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To my father – Who would have been so proud
and my mother –Who made it happen

ABSTRACT

Approximately 120 people die every year due to fires in Sweden. A majority of the fire victims die due to toxic fire gases. Carbon monoxide is often thought to be the major cause of death. Still, another very toxic fire gas, hydrogen cyanide, is formed when materials containing nitrogen burn, e.g. wool or polyurethane foam. The influence of cyanide to fire deaths is difficult to assess due to post mortem break down of cyanide.

Data on carboxyhemoglobin and blood cyanide from deceased fire victims during the period 1992-2009 were collected from two Swedish nationwide forensic databases (ToxBase and RättsBase) (Study IV). The analysis of these data supports the notion that hydrogen cyanide contributes more to the cause of death among fire victims than previously thought.

Cyanide poisoning can be treated with antidotes. Rapid initiation of the treatment is essential. However, no good rapid diagnostic method is currently available. To bridge this gap, we have investigated the possibility of using cyanide in breath as an indicator to cyanide poisoning. In Study I, a low concentration exposure to cyanide showed that the washout of cyanide is rapid. Extrapolating this to a high concentration exposure resulted in that exhaled air, a few minutes after exposure to cyanide, will represent the systemic concentration of cyanide.

In Study II background levels of cyanide in breath was measured in 40 volunteers. The levels ranged from <1.5-14 ppb. Previously published data on background levels of cyanide in breath range from 0 to 62 ppb. In Study III, a physiologically based toxicokinetic model was developed to estimate the levels in exhaled breath after a lethal/near-lethal exposure. The model indicated levels in the range of 0.2-1 ppm. Comparing these results gives more than a twofold difference between unexposed and exposed subject. Thus, indicating that the groups could be separated from one another.

Hence, measurement of exhaled air in fire victims can be used to indicate cyanide poisoning.

LIST OF PUBLICATIONS

I. Washout kinetics of inhaled hydrogen cyanide in breath
Kristin Stamyr, Pierre Nord and Gunnar Johanson
Toxicology Letters, 2008, 179(1):59-62

II. Background levels of hydrogen cyanide in human breath measured by infrared cavity ring down spectroscopy
Kristin Stamyr, Olavi Vaittinen, Janne Jaakola, Joseph Guss, Markus Metsälä, Gunnar Johanson and Lauri Halonen
Biomarkers, 2009; 14(5): 285–291

III. Physiologically-based toxicokinetic modelling of hydrogen cyanide levels in human breath
Kristin Stamyr and Gunnar Johanson
Manuscript

IV. Swedish Forensic Data 1992-2009 Suggest Hydrogen Cyanide as an Important Cause of Death in Fire Victims
Kristin Stamyr, Gunilla Thelander, Lena Ernstgård, Johan Ahlner and Gunnar Johanson
Submitted

CONTENTS

LIST OF ABBREVIATIONS

AOM	Acousto-optical modulator
ATP	Adenosine triphosphate
CCO	Cytochrome C Oxidase
CN^-	Cyanide
CO	Carbon monoxide
CO_2	Carbon dioxide
COHb	Carboxyhaemoglobin
CRDS	near-infrared Cavity ring down spectroscopy
CTIF	International Technical Committee for the prevention and extinction of Fire
DAQ	Data acquisition (card)
H_2O	Water
HCN	Hydrogen cyanide
KCN	Potassium cyanide
MetHb	Methaemoglobin
MSB	Swedish Civil Contingencies Agency
NaCN	Sodium cyanide
NH_3	Ammonia
PBTK model	Physiologically-based toxico-kinetic model
pKa	acid dissociation constant
ppb	parts per billion
ppm	parts per million
SFPA	The Swedish Fire Protection Association
UK	United Kingdom
VRG	Vessel-rich group
WHO	World Health Organization

1 INTRODUCTION

Approximately 120 people die every year due to fires in Sweden (Erlandsson 2007, 2008; McIntyre et al. 2009; Lundqvist et al. 2010). A majority of the fire victims die due to toxic fire gases (Barillo et al. 1986). Carbon monoxide (CO) is often thought to be the major cause of death (Simonson et al. 2001). Still, another very toxic fire gas, hydrogen cyanide (HCN), is formed when materials containing nitrogen burn, e.g. wool or polyurethane foam (Purser 2000; Simonson et al. 2001).

During the past 60 years synthetic polymers, such as polyurethane foam, have been introduced in buildings and furniture (Alarie 2002). Since nitrogen-containing polymers release large amounts of HCN during incomplete combustion (Purser 1992; 1996, 2000) the levels of cyanide in home fires are expected to have increased. Cyanide has been suggested to have a knockdown effect preventing escape and thereby causing death due to CO or both toxins (Purser 2000). Therefore cyanide is suggested as an important or major contribution to fatal outcomes (Purser 2000; Simonson et al. 2001).

Fire victims are routinely treated with oxygen at the fire scene (Baud 2007; Hall et al. 2007). For cyanide poisoning there are available antidotes. However, since there is no available test method for field measurements (Baud 2007; Hall et al. 2007) the actual number of victims suffering from cyanide poisoning is unknown. Forensic data is difficult to use interpret since break down of cyanide occurs post mortem (Moriya et al. 2001; 2003).

Cyanide smells of bitter almonds (Musshoff et al. 2002). Despite this cyanide in breath can be difficult to smell, since concentrations are relatively low, many individuals fail to identify the smell and remaining fire smoke in the airways is likely to mask any smell of cyanide (Baud 2007). Still, the exhaled breath is an interesting possibility for identification. Breath sampling is in general easier to perform than blood sampling, as it is non-invasive.

However, more knowledge on the toxicokinetics of cyanide is required to establish a dose-response relationships. Among the things needed to be investigated is the concentration of HCN in breath after life-threatening exposure levels. Since such relations cannot, be studied experimentally in humans, physiologically-based toxicokinetic (PBTK) modelling offers an interesting and potentially useful alternative. Also, expected background levels in the normal population are of high interest as a comparison with the above mentioned data.

Another kinetic measure needed to be investigated is the relation between cyanide in exhaled air and cyanide in blood versus cyanide in the exposure (the washin – washout effect). This to make sure that potential measurements in exhaled air after a exposure to high levels of cyanide, represent the body burden and not the actual concentration of the recently ended exposure.

2 RESEARCH AIMS

2.1 OVERALL AIM

The overall aim of the thesis was to evaluate the possibility of using exhaled air as a rapid and non-invasive method to identify cyanide poisoning. Additionally the method need to be appropriate for a specific patient group: fire victims.

2.2 SPECIFIC AIMS

I. To study the importance of the washin–washout effect for inhaled HCN in order to determine if exhaled breath can be used to evaluate the systemic levels of cyanide.

II.

a. To measure the background levels of HCN in the breath of a healthy population. Such data is needed as a baseline for future comparison with the levels of poisoned patients.
b. To test the cavity ring down spectroscopy instrument as a method for cyanide breath measurements.

III. To develop a physiologically based toxicokinetic model for inhalation exposure to HCN in humans, with the purpose to estimate the concentration of HCN in breath at lethal or near-lethal exposures.

IV. To investigate the impact of HCN in relation to CO as a cause of death in fire victims, which would serve as an indication as to the importance of treatment of cyanide poisoning in fire victims.

3 CYANIDE

The toxic effect of cyanide and cyanogenic glycosides has been known of for thousands of years (Cummings 2004) and hydrocyanic acid was isolated by Scheele already in 1782 (Cummings 2004). Cyanide exists in a wide variety of chemical structures with the CN^- anion as a common moiety. Exposure can occur via solid, liquid or gas form. The sources can be natural, anthropogenic or originate from industrial production (WHO 2004).

Potassium cyanide (KCN) and sodium cyanide (NaCN) are two out of may examples of cyanide salts. Several of them are used in gold and silver industries, dyeing, printing, photography, electroplating and in the steel industry. They are also used in the synthesis process of organic and inorganic chemicals (Montelius et al. 2001; WHO. 2004).

Hydrogen cyanide gas is a colourless or light blue gas. As a fluid, hydrogen cyanide is very volatile and inflammable (Montelius et al. 2001; WHO 2004). Hydrogen cyanide smells of bitter almonds. The odour threshold has been estimated to 0.2-5 ppm (Musshoff et al. 2002). Yet, many individuals are unable to smell HCN at all (Holland et al. 1986).

3.1 CHEMICAL PROPERTIES

Cyanide is a weak acid with an acid dissociation constant (pKa) of 9.22 at 25°C WHO 2004). Other physical properties can be found in Table 3.1.1.

Table 3.1.1 - Chemical properties of cyanide[1]

	Hydrogen Cyanide	Sodium cyanide	Potassium Cyanide
CAS number	74-90-8	143-33-9	151-50-8
Chemical structure	HCN	NaCN	KCN
Molecular weight	27	49	65
Boiling point (°C)	26	1500	-
Melting point (°C)	-13	570	630
Vapour pressure (kPa, 20°C)	84	-	-

[1](Montelius et al. 2001)

Conversion factors for HCN are:
1 mg/m^3 = 0.89 ppm (20°C)
1 ppm = 1.12 mg/m^3 (20°C)

3.2 EXPOSURE TO CYANIDE

HCN is formed during incomplete combustion of nitrogen containing polymers, for instance from polyurethanes, melamine and wool and can therefore be found in fire gases (Purser 2000). HCN can also be found in cigarette smoke (Roemer et al. 2004).

Exposure to cyanide can also originate from different food stuff, via cyanogenic glycosides. Cyanide is formed as the cyanogenic glycosides break down in the intestines. (Montelius et al. 2001). Examples of food that contain cyanogenic glycosides are: Cassava/(manioc, tapioca), bitter almonds, passion fruit, bamboo sprout, bean sprout, linseed and in kernels of apricot, cherries, peaches and plums (Montelius et al. 2001; WHO 2004). Since cyanide is used as a fumigant, traces can also be found in other food.

The general public is normally exposed to low levels of HCN. Groups with higher exposure are smokers, and workers involved in cassava production or industries using cyanide (Montelius et al. 2001; Roemer et al. 2004; WHO 2004). Sodium nitroprusside is a vasodilation drug used to lower the blood pressure. One downside with this medical drug is that it can lead to cyanide poisoning as it breaks down in the blood stream (Schulz et al. 1982; Lundquist et al. 1989).

3.2.1 Kinetics

HCN, KCN and NaCN are rapidly adsorbed via the lungs and the gastro-intestinal tract. Cyanide can easily be absorbed through the skin (Montelius et al. 2001).

When cyanide has entered the blood it will be reversibly bound to the methaemoglobin (MetHb) in the erythrocytes, and via the blood cyanide can be effectively distributed to the body. Cyanide in plasma may be metabolised, for instance in the liver, kidneys and nose epithelia (Montelius et al. 2001). Eighty percent of the biotransformation takes place via the sulphur transferase enzyme rhodanase and other sulphur transferases to e.g. thiocyanate (Montelius et al. 2001). The availability of the sulphur substrate is therefore important for the elimination of cyanide from the body (Montelius et al. 2001). Thiocyanate is excreted in urine (Lundquist et al. 1979; 1995). Smokers have been seen to excrete more thiocyanate than non-smokers (Chandra et al. 1980).

3.2.2 Backgrounds levels of cyanide

For instance, *Helicobacter pylori*, the bacteria causing gastric ulcer, has been shown to produce cyanide which is detectable in breath (Graham et al. 1987). Another cyanide producing bacteria is *Pseudomonas aeruginosa* (Castric 1975; Carroll et al. 2005). Cyanide in breath may also originate from bacteria, foods containing cyanogenic glycosides, tobacco smoke and inhalation of fire gases (Boxer et al. 1952; Stelmaszynska 1985; Lundquist et al. 1988; Jones 1998; Alarie 2002; Roemer et al. 2004; Carroll et al. 2005; Lechner et al. 2005; 2006; Španěl et al. 2007a; b; Wang et al. 2008). Also cigarette smoking give rise to cyanide exposure (Roemer et al. 2004).

Backgroundlevels of cyanide in breath range from 0 – 62 ppb (Lundquist et al. 1988; Španěl et al. 2007a;b; Wang et al. 2008).

3.3 TOXICITY

Cyanide is highly toxic independent of the route of exposure. The dose-effect curve is very steep (WHO 2004). Haber's law states that the relationship between the

concentration of a poisonous gas and the time required to reach a certain effect is constant, see Equation 3.3.1.

$$C \cdot t = k \qquad \text{(Equation 3.3.1)}$$

where, *C* represents the concentration, *t* represents the required time to reach the effect in question, *k*. However, as cyanide does not follow Haber's law (Montelius et al. 2001), extrapolations from high to low doses are difficult to perform.

3.3.1 Mode of action

Cyanide is toxic to the body by its ability to block the cellular respiration, leading to anoxia WHO 2004). Cytochrome C Oxidase (CCO), at the end of the electron transport chain, converts oxygen to water. This process leads to production of adenosine triphosphate (ATP). Cyanide in blood will reduce this process by binding the ferric ion portion of CCO. Since ATP is the primary source of energy for the cell, the reduction will lead to cellular dysfunction or cellular death (Nelson 2006). In other words, cyanide poisoning leads to inability of the cell to use available oxygen in the blood stream. This may lead to venous blood with high oxygen levels. Also high plasma lactate levels can be seen as the cell will produce energy via the less effective anaerobic metabolism pathway (Nelson 2006). Target organs for cyanide poisoning are the central nervous system as well as the respiratory and cardiovascular systems WHO 2004).

Toxicity due to chronic exposure is thought to be causes by toxicity from thiocyanate, a byproduct from cyanide metabolism (WHO 2004). Here a potential target organ is the endocrine system (WHO 2004).

Chronic exposure to cyanogenic glycosides has resulted in tropical ataxic neuropathy and spastic paraparesis. In combination with low iodine status hypothyroidism, goiter and cretinism have been seen (WHO 2004).

4 FIRES

One major exposure to cyanide in via fire smoke. Cyanide is yielded when nitrogen containing materials burn especially during and incomplete burning process (Purser 2000).

In a fire there are many hazards. Not only toxic fire gases may pose a threat, smoke, heat and lack of oxygen are also important factors affecting the chance of survival (Erlandsson et al. 1999; Purser 2000). Figure 4.1 shows a well-developed fire that poses all of the mentioned treats.

Figure 4.1 - Fire in industrial premises **Photo: Karl Andersson**

A fire has a great negative impact on the general condition of a person. This will be manifested in several ways. A fire will give rise to heat and an elevated body temperature, also resulting in reduced state of consciousness and brain damage. Contact with hot objects and hot air can cause swelling and burns in the respiratory tract (Erlandsson et al. 1999; Purser 2000).

Heat and burns may lead to negative effects on the circulatory system and severely affect the homeostasis. Burns can also result in decompositions of the red blood cells. However, in an unconscious patient exposed to fires, fire gas intoxication (e.g. by cyanide) can be strongly suspected. Heat, irritation, pain and toxic fire gases will impair a person's possibilities to escape a fire (Erlandsson et al. 1999; Purser 2000).

Exposure to toxic fire gases can also give lead to elevated methaemoglobin levels. This will reduce the oxygen carrying capacity (Erlandsson et al. 1999; Purser 2000).

4.1 OXYGEN DEFIENCY

To compensate for hypoxia, due to reduced amount of oxygen in the air, the blood flow to the brain will increase. This can indirectly lead to increased toxic exposure to the brain (Erlandsson et al. 1999; Purser 2000).

The following symptoms can be seen depending on the severity of the hypoxia: Increased breathing frequency, increased heart rate, impaired ability of judgement, impaired short term memory, stupor and shock (Erlandsson et al. 1999).

4.2 CO

Carbon monoxide (CO) is produced in high concentrations by incomplete combustion of carbon-containing compounds. CO is commonly thought to be the major cause of most fire-related intoxications and deaths (Simonson et al. 2001). CO has approximately 220 times higher affinity than oxygen for haemoglobin and displaces the oxygen by forming carboxyhaemoglobin (COHb). The resulting reduced oxygen supply capacity may lead to unconsciousness, convulsions, cardiovascular collapse followed by shock, and asphyxia. Mental and muscular performance is impaired at about 30% COHb and fainting may occur (Alarie 2002). Levels above 50% are severely toxic and the fatal threshold has been assumed to be 50% (Anderson et al. 1981a, b) However, also levels above 70% COHb have been suggested (Widdop 2002) as a lethal threshold.

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4.3 HCN

Hydrogen cyanide (HCN) is another toxic gas that is generated during fires. HCN is formed during incomplete combustion of materials containing nitrogen, such as polyurethane foam, synthetic rubber, melamine, silk and wool (Purser 2000; Simonson et al. 2001). Nitrogen-containing polymers release great amounts of hydrogen cyanide (HCN) during incomplete combustion (Purser 1992; 1996; 2000).

These materials are increasingly being used in homes and other indoor environments (Alarie 2002). The combustion conditions, oxygen supply and composition of the organic materials are crucial for the concentrations of HCN and CO (Purser 1992).

Symptoms of cyanide poisoning are: rapid breathing, vertigo, confusion, headache, nausea, vomiting, fatigue, impaired muscle coordination, respiratory distress, cardiac arrhythmias, spasms, unconsciousness and death (Montelius et al. 2001).
Table 4.3.1 presents time to death for different HCN concentrations.

Table 4.3.1 - Exposure concentration – duration relationship for human inhalation exposure to hydrogen cyanide

Exposure level (ppm)	Time to death (min)	References
110	60	Flury et al. 1931
135	30	Hall et al. 1986
181	10	Hall et al. 1986
270	7	Flury et al. 1931

4.4 STATISTICS – FIRE DEATHS

Statistics on fire fatalities offers a possibility to evaluate the need of better means to diagnose cyanide poisoning in fire victims.

4.4.1 Sweden

Approximately 120 people die every year due to fires in Sweden (Erlandsson 2007, 2008; McIntyre et al. 2009; Lundqvist et al. 2010). This corresponds to 8-20 persons per million inhabitants see Table 4.4.1.

Table 4.4.1 - Number of fire deaths in Sweden

Year	*Number of fire deaths according to data in Study IV*	*Number of fire related deaths according to Swedish Civil Contingencies Agency – MSB*[1,2]
1992	135	134
1993	129	119
1994	116	126
1995	128	107
1996	124	131
1997	161	152
1998	181	177
1999	104	110
2000	123	107
2001	149	133
2002	152	138
2003	146	134
2004	95	65
2005	106	104
2006	105	83
2007	110	97
2008	119	115
2009	120	114
Total	2303	2146

[1,2] - (McIntyre et al. 2009; Lundqvist et al. 2010)

The following criteria, valid from 1999, define what is to be considered a fire fatality (Harrami et al. 2006; Erlandsson 2008):

- the person must have died due to a fire or an explosive combustion process
- death must have occurred within a month after the fire
- it must be concluded that the victim was alive when the fire gases or the flames reached the body if the victim is involved in an accident or can be suspected to have died due to illness, electricity or other causes

The report of fire deaths is done by the local emergency services, fire investigators, police investigating fires, surveillance of the media, The Swedish Fire Protection

Association (SFPA) and investigators of traffic accidents. In some cases information will be retrieved from The National Board of Forensic Medicine (Erlandsson 2008).

The most common cause of a fire with deadly outcome is carelessness when smoking (25% in 2000-2004) (Harrami et al. 2006). In at least 61% of the fatal domestic fires no smoke detectors were present (2000-2004) (Harrami et al. 2006). Men have a higher risk than women of dying in fires. Also elderly people are over-represented (Harrami et al. 2006). Elderly and marginalized individuals together stand for at least 60 % of the fire fatalities (Harrami et al. 2006). The death rate has fallen with approximately 35% since 1945. It is not exactly known why, however, decline in the smoking population is suspected as one reason. It has been noted that death rates from males between the ages 15-64 due to burns have decreased since 1945 (Harrami et al. 2006). Statistically, for every fire fatality in Sweden it is estimated seven victims with serious injuries as well as seven with minor injuries (Harrami et al. 2006).

It has been noted by experts and fire fighters that the development of a fire has become more rapid since the 1960s. This change is attributed to the increasing amount of plastics included in our homes (Harrami et al. 2006).

The main strategy in Sweden to reduce fires has been information to increase awareness of fire. Further approaches are efforts to increase the amount of homes with functioning smoke detectors as well as the building laws stating that a house should be built so that a fire will not spread between houses or apartments within the first hour (Harrami et al. 2006).

4.4.2 Other parts of the world

Since fires occur all over the world, cyanide poisoning in fire victims is not a problem isolated to Sweden. Comparable statistics for the whole world is difficult to find. However, The Geneva Association, an international “think tank” for strategically important insurance and risk management issues (Paish 2010) publish summaries of fire statistics from selected countries every year. Their data is collected by a questionnaire sent to national correspondents and data that is available from The World Health Organisation (Paish 2010).

It is difficult to evaluate the validity of the whole dataset since it is not specified how each and every country count and report their data. Still, it is likely that the report from each country is conducted in a similar way over time. A combination of 13 reports is presented in Table 4.4.2 and Table 4.4.3. Most of the data appears to be rounded to the nearest 0-5-10 value. Every report presented data for a three-year period. On a few occasions data in two successive years did not correspond to each other. In such cases, the data from the most recent report was chosen. The number of fire victims in 24 different countries over the time period 1992 – 2007 can be studied in Table 4.4.2.

To enable a better comparison between the 24 countries Table 4.4.3 presents the same dataset however normalised for the total population of the countries. The population data was retrieved from two annual United Nation reports. Population data for 1992-1998 from the 2001 Demographic Yearbook (United Nations. Statistical Office 2003)

and 1999-2007 from the 2008 Demographic Yearbook (United Nations. Statistical Office 2010). There is some overlap in these two data sets. Where there were deviations between the 2001 and the 2008 yearbook the data from the 2008 yearbook was selected.

Another organisation that publishes fire statistics is CTIF (International Technical Committee for the prevention and extinction of Fire). In 2000 they made a report on worldwide fire data (Brushlinski et al. 2000). Their data show a wide spread in number of deaths per million inhabitants. Represented among the countries with the highest values for fire deaths per inhabitants are several countries from Eastern Europe, for example Estonia and Russia with over and just below 100 fire deaths per year and one million inhabitants, respectively (Brushlinski et al. 2000). In the same report the average value for the whole world was estimated to be 10 fire deaths per million inhabitants.

Table 4.4.2 – International fire death statistics, number of victims

	1992[1]	1993[2]	1994[3]	1995[4]	1996[4]	1997[5]	1998[6]	1999[7]	2000[8]	2001[9]	2002[10]	2003[11]	2004[12]	2005[13]	2006[13]	2007[13]
Australia	175	165	135	135	145	110	140	140	145	105	135	135	110	140	90	100
Austria	65	60	70	60	65	76	55	55	225	55	40	45	50	45	30	30
Canada	440	460	415	440	410	460	370	425	360	370	335	-	-	-	-	-
Czech	130	100	110	115	125	140	100	110	105	105	115	150	130	145	150	135
Denmark	90	75	90	90	105	74	79	846	876	75	75	90	85	85	70	70
Finland	-	130	120	95	110	105	91	105	95	85	95	105	110	85	125	95
France	645	725	610	585	645	530	580	575	555	550	-	645	585	660	620	605
Germany	910	875	745	770	895	730	650	630	590	600	-	545	560	605	510	-
Greece	200	170	160	150	140	160	145	120	190	190	145	150	145	140	100	265
Hungary	315	365	335	300	290	255	205	190	200	235	195	210	195	195	180	175
Ireland	-	-	-	-	-	73	61	85	60	70	60	40	40	45	40	55
Italy	-	-	-	455	-	475	435	420	410	355	-	270	-	-	280	250
Japan	1920	1880	1940	2400	2020	2150	2100	2150	2050	2250	2300	2300	2050	2250	2100	2050
Netherlands	95	90	100	85	130	-	-	-	-	-	-	-	-	70	85	70
New Zeeland	30	40	35	35	40	38	53	376	336	40	40	40	30	30	25	35
Norway	75	65	55	65	70	68	53	616	576	65	65	55	55	65	-	-
Poland	645	595	595	590	620	570	505	560	515	510	455	525	485	590	605	600
Singapore	-	-	-	-	5	9	11	26	76	10	0	0	10	5	10	-
Slovenia	-	-	10	30	30	30	22	15	15	20	20	25	20	2011	-	-
Spain	335	-	310	210	-	260	250	275	260	265	230	280	275	280	245	235
Sweden	110	120	120	105	125	130	180	115	110	145	145	140	70	110	90	100
Switzerland	45	35	35	20	35	62	41	40	40	-	-	35	40	35‡	30‡	15‡
UK	895	790	705	770	745	760	690	580	645	635	590	625	535	515	515	465
USA	5100	5000	4650	5000	5400	4400	4400	3900	4400	6900†	3700	4300	4250	4000	3550	3750

†2791 from 9/11 are included, ‡not including fire fighters deaths; deaths in buildings only

[1](Wilmot 1997), [2](Wilmot et al. 1998), [3](Wilmot et al. 1999), [4](Wilmot et al. 2000), [5](Wilmot et al. 2002a), [6](Wilmot et al. 2002b, 2003), [7](Wilmot et al. 2004), [8](Wilmot et al. 2005), [9](Wilmot et al. 2006), [10](Paish 2007), [11](Paish 2008), [12](Paish 2009), [13](Paish 2010)

Table 4.4.3 - International fire death statistics, number of victims per 1 000 000 inhabitants

	1992[1]	1993[2]	1994[3]	1995[4]	1996[4]	1997[5]	1998[6]	1999[7]	2000[8]	2001[9]	2002[10]	2003[11]	2004[12]	2005[13]	2006[13]	2007[13]
Australia	10.1	9.4	7.6	7.5	7.9	5.9	7.5	7.4	7.6	5.4	6.9	6.8	5.5	10.1	9.4	7.6
Austria	8.3	7.6	8.8	7.5	8.0	9.4	6.8	6.9	28.1	6.8	4.9	5.5	6.1	8.3	7.6	8.8
Canada	15.5	16.0	14.3	15.0	13.8	15.4	12.2	14.0	11.7	11.9	10.7	-	-	15.5	16.0	14.3
Czech	12.6	9.7	10.6	11.1	12.1	13.6	9.7	10.7	10.3	10.3	11.3	14.7	12.8	12.6	9.7	10.6
Denmark	17.4	14.5	17.3	17.2	20.0	14.0	14.9	15.8	16.3	14.0	14.0	16.7	15.7	17.4	14.5	17.3
Finland	-	25.7	23.6	18.6	21.5	20.4	17.7	20.3	18.4	16.4	18.3	20.1	21.0	-	25.7	23.6
France	11.3	12.6	10.5	10.1	11.0	9.0	9.9	9.8	9.4	9.3	-	10.7	9.6	11.3	12.6	10.5
Germany	11.3	10.8	9.2	9.4	10.9	8.9	7.9	7.7	7.2	7.3	-	6.6	6.8	11.3	10.8	9.2
Greece	19.5	16.5	15.4	14.3	13.3	15.0	13.5	11.0	17.4	17.3	13.2	13.6	13.1	19.5	16.5	15.4
Hungary	30.6	35.5	32.7	29.4	28.5	25.1	20.3	18.5	19.6	23.1	19.2	20.7	19.3	30.6	35.5	32.7
Ireland	-	-	-	-	-	19.8	16.4	22.7	15.8	18.1	15.2	10.0	9.7	-	-	-
Italy	-	-	-	7.9	-	8.3	7.6	7.4	7.2	6.2	-	4.7	-	-	-	-
Japan	15.4	15.1	15.5	19.1	16.1	17.0	16.6	17.0	16.2	17.7	18.1	18.1	16.1	15.4	15.1	15.5
Netherlands	6.3	5.9	6.5	5.5	8.4	-	-	-	-	-	-	-	-	6.3	5.9	6.5
New Zeeland	8.7	11.4	9.8	9.7	11.0	10.3	14.3	9.7	8.5	10.2	10.1	10.0	7.4	8.7	11.4	9.8
Norway	17.5	15.1	12.7	14.9	16.0	15.4	12.0	13.7	12.7	14.4	14.3	12.0	12.0	17.5	15.1	12.7
Poland	16.8	15.5	15.4	15.3	16.0	14.7	13.1	14.6	13.4	13.3	11.9	13.7	12.7	16.8	15.5	15.4
Singapore	-	-	-	-	1.4	2.4	2.9	0.5	1.7	2.5	0.0	0.0	2.4	-	-	-
Slovenia	-	-	5.1	15.1	15.0	15.0	11.0	7.6	7.6	10.1	10.0	12.5	10.0	-	-	5.1
Spain	8.5	-	7.8	5.3	-	6.5	6.2	6.9	6.5	6.5	5.6	6.7	6.5	8.5	-	7.8
Sweden	12.7	13.7	13.7	11.9	14.1	14.7	20.3	13.0	12.4	16.3	16.2	15.6	7.8	12.7	13.7	13.7
Switzerland	6.5	5.0	4.9	2.8	4.9	8.7	5.7	5.6	5.6	-	-	4.8	5.4	6.5	5.0	4.9
UK	15.7	13.8	12.3	13.3	12.9	13.1	11.8	9.9	10.9	10.7	9.9	10.5	8.9	15.7	13.8	12.3
USA	19.5	18.9	17.4	18.5	19.8	15.9	15.8	13.7	15.3	23.7	12.6	14.5	14.2	19.5	18.9	17.4

[†]2791 from 9/11 are included, [‡]not including fire fighters deaths; deaths in buildings only

[1](Wilmot 1997), [2](Wilmot et al. 1998), [3](Wilmot et al. 1999), [4](Wilmot et al. 2000), [5](Wilmot et al. 2002a), [6](Wilmot et al. 2002b, 2003), [7](Wilmot et al. 2004), [8](Wilmot et al. 2005), [9](Wilmot et al. 2006), [10](Paish 2007), [11](Paish 2008), [12](Paish 2009), [13](Paish 2010) – Population data 1992-1998 from (United Nations. Statistical Office 2003) and 1999-2007 from (United Nations. Statistical Office 2010)

4.4.3 Discussion – Fire statistics

Comparing fire statistics between countries is not always an easy task. There can be both differences in inclusion criteria as well as different ways of retrieving information on the victims. However, it is still important to be able to follow national statistics over the years to better evaluate preventive actions.

Table 4.4.1 shows data on fire death statistics in Sweden. It shows that the data from Study IV is generally somewhat higher than the data from Swedish Civil Contingencies Agency (MSB). Firstly, there is a slight difference between sources. The data in Study IV is based on all medicolegal autopsies during the period, while the MSB data was retrieved according to their channels. Secondly, there is a difference in actual dating of the data: MSB data is dated the year of the fire[1] and data in Study IV is dated based on the date the forensic analysis was made. As fire deaths during the winter months are more common than during the summer months (McIntyre et al. 2009), this might be a reason for this difference. Still, it can be noted that the total number of fire deaths during the period is about 10 % higher in Study IV compared to MSB data.

MSB has, independently of Study IV, started an inventory of their data. MSB has connected their database with The National Board of Forensic Medicines databases (the same as in Study IV) as well as The National Board of Health and Welfare's registry on cause of deaths. Preliminary data shows that about 26% of Swedish fire deaths were missed in the previous system for recording fire deaths[1].

[1](Personal communication Anders Jonson MSB, October 2011).

4.5 DIAGNOSE, SYMPTOMS AND TREATMENT

Unconscious patients from a fire are always treated with 100% oxygen in Sweden. Antidotes can be used if cyanide poisoning is suspected. Common antidotes in Sweden are hydroxocobalamine (Cyanokit) or Sodium thiosulphate (Erlandsson et al. 1999). Rapid initiation is required best treatment results. Since no rapid direct diagnosis method is available indirect methods are used. A typical clinical laboratory finding in acute cyanide poisoning is metabolic acidosis with markedly elevated plasma lactate levels (Borron 2006; Baud 2007). Since sooty fires often give rise to high levels of HCN the presence of soot in the airways also can be used as an indication of cyanide poisoning (Lawson-Smith et al. 2011).

4.5.1 Antidotes

A number of antidotes are used or have been proposed for treatment of cyanide poisoning. Cyanide antidotes can be divided into four different main groups: methaemoglobin-forming substances (e.g. amyl nitrite), cobalt compounds (e.g. hydroxocobalamin), sulphur donors (e.g. sodium thiosulphate) and cyanohydrin-forming agents (e.g. alpha-ketoglutarate) (Hall et al. 1989; 2007; Bhattacharya et al. 2002; Baud 2007;).

Methaemoglobin-forming substances

Amyl nitrite will react with haemoglobin to form methaemoglobin. Cyanide will bind reversibly to methaemoglobin and thereby reduce the toxicity. However, in the particular case of fire victims, more methaemoglobin is not recommended, since it will further reduce the oxygen carrying capacity of the blood (Holland et al. 1986).

Cobalt compounds (e.g. hydroxocobalamin),

Hydroxocobalamin is a precursor to vitamin B12, and will bind cyanide on one to one molar basis. Cyanokit is an antidote based on hydroxocobalamin and will attract cyanide more than cytochrome oxidase (Hall et al. 2007).

Sulphur donors

Sodium thiosulphate can be used as a substrate for the sulphur-substrate dependent metabolism since it is transferring cyanide into thiocyanate (Cummings 2004).

Cyanohydrin-forming agents

Alpha-ketoglutarate is an example of a cyanohydrin forming agent. A downside with this antidote is that it itself has toxic properties and therefore is suitable only when cyanide poisoning is confirmed. (Bhattacharya et al. 2002; 2004).

Hydroxocobalamin and sodium thiosulphate have been suggested as the preferred antidotes in fire victims (Hall et al. 1989; 2007).

4.5.2 Discussion – Pre-hospital treatment

To enable better treatment for fire victims it is essential that the victims receive relevant treatment as soon as possible, ideally already at the fire site as a part of the pre-hospital treatment. It is vital that diagnose can be made as soon as possible.

Figure 4.2 - A Swedish ambulance. Possibly not the best transport vehicle of a cyanide-diagnose equipment.
Photo: Kristin Stamyr

Both fire trucks and ambulances are equipped with oxygen. At least in Stockholm ambulances are also equipped with thiosulphate. However, Cyanokit is only available in special ambulances usually ordered to the fire site and therefore delaying the process. On the other hand, every single ambulance in the Stockholm area do not have the need for Cyanokit very often, see Figure 4.2. Therefore equipping all ambulances with Cyanokit is probably not the best idea. Additionally, if there is a big fire the ambulance might don´t carry enough antidotes.[1]

If a small, mobile, easy to use device for diagnose of cyanide poisoning is developed possibly the ambulances are not the best place to put it. A better idea could be in the fire trucks, see Figure 4.3. For instance in the Stockholm area there are just below 60 ambulances and about five fire command cars (befälsbilar). The fire captain/outer chain of command will be called to all verified apartment fires. One idea could be that the fire department will bring both detector and antidotes. Even though it may be administratively difficult to motivate that the fire department should carry equipment that they will not use and also to carry drugs that they are not allowed administer. Still if one can overcome these potential administrative obstacles collaboration between the fire department and the ambulance services might bring a good practical solution to the problem. [1]

[1]Personal communication. Kjell Berglöf, fire captain/outer chain of command (överbrandmästare/yttrebefäl) and co-workers at Vällingby fire station, Oktober 2011.

Figure 4.3 - A Swedish fire truck, possibly a solution for transportation of a future cyanide diagnose equipment and antidote **Photo: Kristin Stamyr**

5 THE WASHIN-WASHOUT EFFECT

The epithelial lining of the respiratory tract is coated with a thin mucus layer in which chemical vapours can dissolve during inhalation (washin). Hence, during exhalation such chemicals can diffuse back to the respiratory tract (washout). This process is referred to as the washin-washout effect.

The washin-washout effect is generally neglectable for non-polar chemicals where the measurements of the chemical substance in the exhaled air will only represent the systemic concentration of the chemical. However, for polar substances the washin-washout effect may be substantial and the measured levels will then represent a combination of the external exposure and the systemic concentration. This is why it is important to have information of the size of the washin-washout effect when performing breath measurements after inhalation exposure.

One way to estimate the size of the washin-washout effect is to evaluate the half-life of the chemical substance by performing a controlled inhalation exposure study. In such a study subjects are exposed via inhalation to known air-concentrations of the substance while the amount in exhaled air is monitored. This was done in Study I (Figure 5.1)

The half-life is dependent on the mass flow (alveolar ventilation) and diffusion of the chemical in the mucosa. Thus, it is proportional to the exposure level. Therefore, the kinetics of the washin-washout effect can be extrapolated to high exposure scenarios, based on the results from a low exposure study.

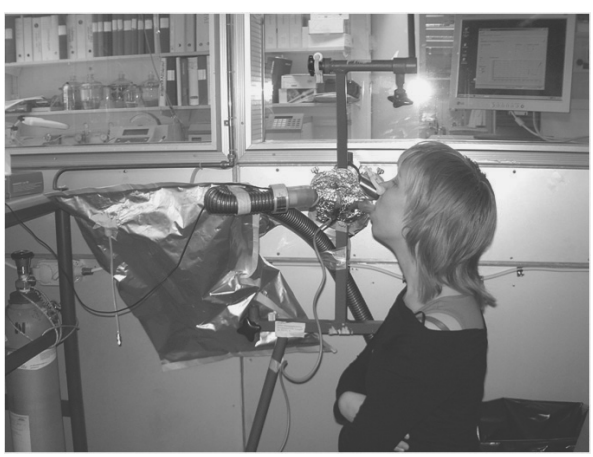

Figure 5.1 - A controlled low concentration exposure to hydrogen cyanide, to enable evaluation of the washin-washout effect

The washin-washout effect has been described for several different chemicals, in human (Landahl et al. 1950; Schrikker et al. 1985; Johanson 1991; Mörk et al. 2006;. 2009) and animal studies (Morris et al. 1986a; b).

6 KINETIC MODELLING

To evaluate human risks, associated with exposure to toxic substances, a number of assumptions, estimations and extrapolations are often required. On many occasions the evaluations need to be based on animal data, alternative exposure routes (e.g. oral instead of inhalation) or doses in a different dose range. In these cases extrapolations are necessary (Clewell et al. 2008).

Modelling of kinetic data can be divided into two different model groups: descriptive models and physiologically based models. Descriptive models are often based on already existing data that the model is fitted to, so called best fit. This type of modelling may give a very good description of the data. However, it can be difficult to draw conclusions outside the range of the data set i.e. no new data is generated (Nestorov 2003).

One way to do extrapolations or to draw wider conclusions from the dataset could be by using a physiologically-based toxicokinetic model (PBTK modelling). The method is based on physiological and biochemical descriptions of the species in question as well as chemical-specific data (Clewell et al. 2008).

6.1 PHYSIOLOGICALY BASED TOXICO KINETIC MODELLING

In a PBTK model, the body is described by dividing it into different compartments. Every compartment represents and organ, a part of an organ or a group of organs. The number of compartments used depends on the available data and the chemical in question. One compartment for each and every organ in the body, might give a very good description. However, for a complicated model it will be difficult to find data on all required parameters. If not enough good data is available, the value of the use of many compartments will be reduced. Generally, one tries to keep the model as simple as possible for instance by grouping organs with similar properties together (Nestorov 2003; Clewell et al. 2008).

Normally, it is assumed that the chemical behaves according to the “well-stirred” model, meaning that the chemical is spread evenly and immediately within a compartment. This is often a good approximation. There are also models where a chemical concentration gradient over the organ is assumed. In these cases a better description can be made by dividing the organ into several sub-compartments. For example, for inhaled polar solvents it is sometimes required to divide the lung into several compartments (Johanson 1991; Mörk et al. 2006). Another example is the model in Study II, where blood has been divided into a plasma and an erythrocytes section based on the very different affinity of cyanide.

Creating a PBTK model can be accomplished in the following way (Nestorov 2003):

1) Specify the model structure
2) Create equations
3) Estimate required parameters

1) *Specify the model structure*
   PBTK models require that you have a hypothesis about the substrate mechanisms. In PBTK models data, mechanisms and choice of compartments are determined before the model is created, while in conventional models, these

parameters are chosen according to how they fit the available data (Nestorov 2003).

As PBTK models are based on anatomical assumptions like blood flows and properties of the different organs, it is important to have some basic knowledge about the toxicokinetics and toxicodynamics of the chemical. In Figure 6.1 a schematic description of hypothetical PBTK model with exposure over the inhalation route is presented. In a PBTK model the blood circulation in the body is often represented by an arterial and a venous part. If there are several exposure routes one compartment for each route can be chosen. Exposure to a gas might lead to exposure both from the skin and the lungs for some chemicals.

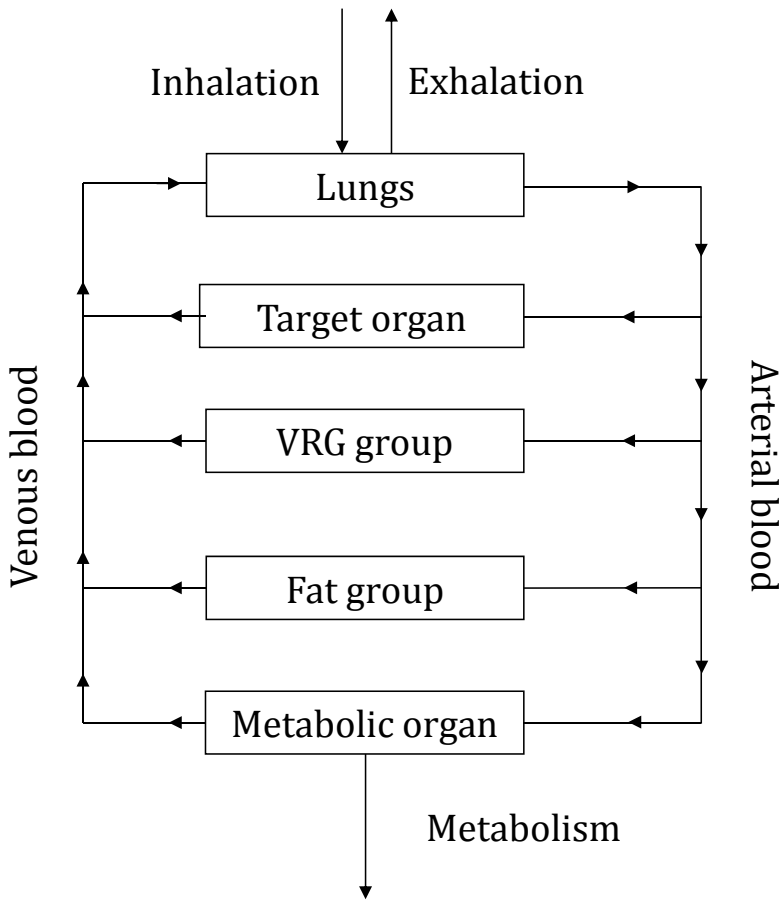

Figure 6.1 - Schematic description of a PBTK inhalation model

If the target organ is known, and sufficient physiological data is available a compartment for this organ may be very useful. The excretion from the body could take place as exhalation via the lungs or after metabolism, for instance in the liver or in the kidneys. The organs left are often lumped together, depending

on their physiological properties. Two examples of common grouping are VRG (vessel-rich group), and the Fat group.

2) *Create equations*
The flows between the different compartments are represented by arrows. And these flows are described by setting up a mass balance and constructing differential equations. In Figure 6.1.2 a two-compartment model is presented and in Equation 6.1.1 and 6.1.2 the differential equations to this model are presented. Where C represents concentrations, Q flow, $P_{B/A}$ partition coefficient, k_A clearance and V compartment volumes.

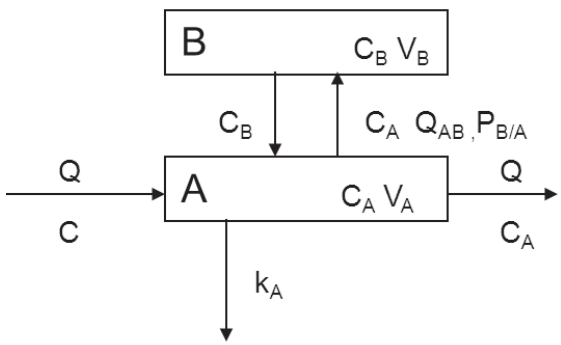

Figure 6.1.2 – A two- compartment model with metabolism

$$\frac{dC_A}{dt} = \frac{(Q \cdot C - Q \cdot C_A - Q_{AB} \cdot C_A - k_A \cdot C_A + Q_{AB} \cdot \frac{C_B}{P_{B/A}})}{V_A} \quad \textbf{(Equation 6.1.1)}$$

$$\frac{dC_B}{dt} = \frac{(Q_{AB} \cdot C_A - Q_{AB} \cdot \frac{C_B}{P_{B/A}})}{V_B} \quad \textbf{(Equation 6.1.2)}$$

3) *Estimate required parameters*
Data used in the PBTK models can be divided into equal groups: substrate independent and substrate-specific data. Among the substrate independent parameters are anatomical and physiological data. The substrate-specific parameters describe the specific kinetics of the substrate and are obtained from experimental data (Nestorov 2003).

Typical parameters required are: Compartment specific blood flows, volumes, partition coefficients as well as metabolic parameters and ventilation rates.

After this distribution and concentration profiles can then be estimated by using a software for solving differential equations e.g. Berkley Madonna (Macey and Oster, Berkeley, CA).

When the model is created it has to be validated. Ideally two datasets are used one for construction of the model and one for validation (Clewell et al. 2008).

7 CAVITY RING DOWN SPECTROSCOPY – CRDS

Cavity ring down spectroscopy (CRDS) is a laser-based absorption technique with high sensitivity suitable for trace gas analysis. There are three main components required for a typical absorption experiment: a light source, a sample (in a cell), and a detector, see Figure 7.1.

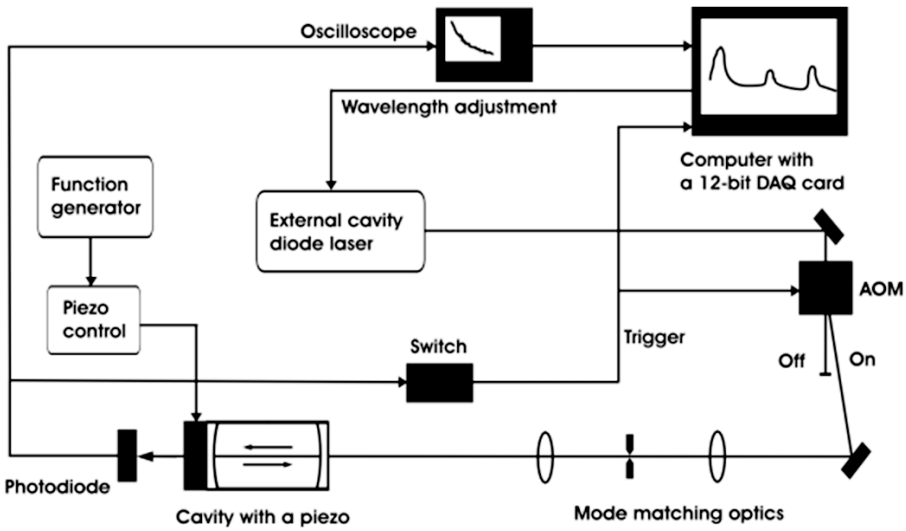

Figure 7.1 - Schematic representation of the cavity ring down spectroscopy experimental setup. Thick lines are laser beams and thin lines are signal cables. The laser beam, generated by the external cavity diode laser, is switched via an acousto-optical modulator (AOM) into the optical cavity. The light leaking from the cavity is detected by a photoreceiver, the signal from which is used to trigger the recording and to turn off the AOM. The signal is processed by the data acquisition card (DAQ) before the computer extracts a time constant and plots the spectrum (Stamyr K, Vaittinen O, Jaakola J, Guss J, Metsala M, Johanson G and Halonen L., Biomarkers, 2009; 14:285-91, copyright © 2009, Informa Healthcare. Reproduced with permission of Informa Healthcare)

The sample gas is kept inside a cavity and a laser pulse is sent into the cavity. In other absorption techniques, it is common to directly measure the transmission. However, in CRDS the absorption is estimated in another way. At each end of the cavity there are one highly reflective mirror, often R>99.9% reflectance. The laser pulse will reflect back and forth many times, which will give a long cavity path length. Increasing the path length is the means of increasing the sensitivity in absorption spectroscopy. A detector is placed at the end of the cavity. This detector measures the leakage from the mirrors. To record a spectral data point, the incoming light is abruptly shut off and for a short period the remaining (and decaying) light is recorded with a photodiode operating as a detector. The shorter is the decay of light (ring-down) the stronger is the absorption of the sample molecules. One of the important advantages of CRDS over other absorption techniques is that the whole exponential decay is measured rather than a single intensity, eliminating the problem with fluctuations in the laser intensity. The result is reduced baseline noise and greater sensitivity. The sensitivity of the spectrometer allows detection of the trace gases even below one ppb level (O'Keefe et al. 1988; Berden et al. 2000; van der Sneppen et al. 2009). Figure 7.2 present a CRDS setup.

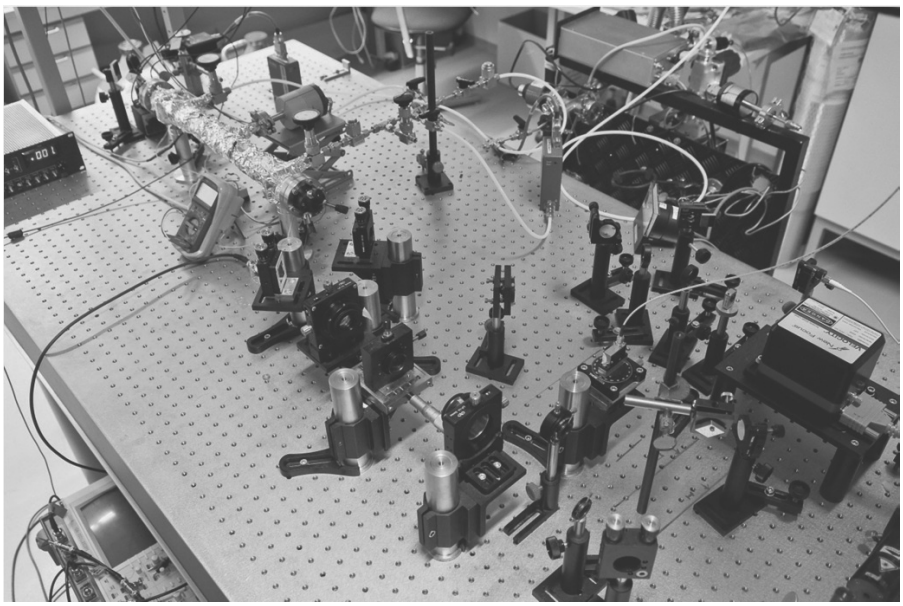

Figure 7.2 - Setup of the CRDS equipment at Helsinki University **Photo: Florian Schimidt**

Form the ring down time the absorption and the concentration can be calculated. By scanning the same sample over a variety of wavelengths several chemicals can be quantified in the same sample e.g. Figure 7.3 (Berden et al. 2000).

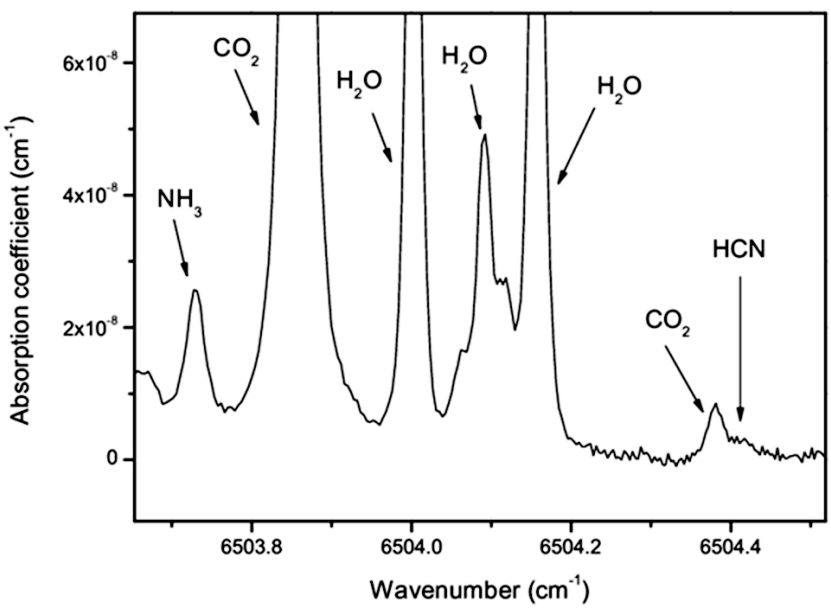

Figure 7.3 - Typical spectrum of the region of interest for hydrogen (Stamyr K, Vaittinen O, Jaakola J, Guss J, Metsala M, Johanson G and Halonen L., Biomarkers, 2009; 14:285-91, copyright © 2009, Informa Healthcare. Reproduced with permission of Informa Healthcare)

In Study II CRDS was used to measure background levels of cyanide in healthy volunteers. The breath sampling procedure can be seen in Figure 7.4.

Figure 7.4 - Breath sampling prior to a CRDS measurement

8 SUMMARY

8.1 THE WASHIN-WASHOUT EFFECT – STUDY I

In Study I the importance of the washin–washout effect for inhaled HCN was investigated. By exposing healthy volunteers to low levels (10 ppm or 11 mg/m^3) of HCN for 1 min, and tracing the profile in exhaled air it was concluded that the disappearance of HCN from the respiratory system is rapid, with a half-life of between 10 and 24 s in exhaled breath. The average half-life in exhaled breath was 15.6 s. Extrapolating the results of Study I to a 1-min exposure at 100 ppm HCN, shows that the breath level would range from 0.0001 to 20 ppb 5min after the end of the exposure. Compared to background levels of cyanide in breath (0-62 ppb) this suggests that the respiratory washout effect of HCN can be neglected. Thus, the concentration of hydrogen cyanide in breath might be used as an indicator of systemic cyanide poisoning.

This is, to our knowledge, the first study that has investigated the kinetics of hydrogen cyanide in breath.

8.2 BACKGROUNDLEVELS OF CYANIDE IN BREATH – STUDY II

A CRDS method was developed for measurement of HCN in breath. This method was used to investigate the background levels of 40 healthy subjects. Participating in the study were 26 men and 14 females in the age group 21-61 years. Of these were 8 smokers. All subjects gave one breath sample which was analysed for HCN, NH_3, CO_2 and H_2O.

The median level of HCN in breath was 4.4 ppb (range <1.5–14 ppb). Five other studies report medians of 15 (3–33) ppb, 10 (0–62) ppb, 6 (1–18) ppb, 13 ppb (4–14) and 4.7 (1.2-12.9) (Lundquist et al. 1988; Španěl et al. 2007a, b; Wang et al. 2008; Schmidt et al. 2011). No correlation was observed with smoking habits, recent meals or age. However, female subjects had slightly higher breath levels of HCN than male subjects.

Ammonia had a median of 210 ppb (range 160–650 ppb), water 1.9% (1.7–2.5%) and carbon dioxide 2.8%, (1.9–4.0%).

In conclusion, CRDS is a useful method for measuring the low background levels of HCN present in breath. The detection limit is sufficiently low and the method is non-invasive. Together with the relatively small sample sizes required and that sample collection is easy to perform, it makes CRDS suitable for breath measurement of HCN. In addition to HCN, the breath components of carbon dioxide, ammonia and water can be measured simultaneously, which adds further to the possibilities for other types of breath-based diagnosis.

CRDS has not previously been used for this purpose.

8.3 PBTK - MODELLING OF HCN – STUDY III

A six compartment PBTK model was developed (Figure 8.1), describing the time course for cyanide in blood, plasma and exhaled breath during and after several simulated cyanide exposures.

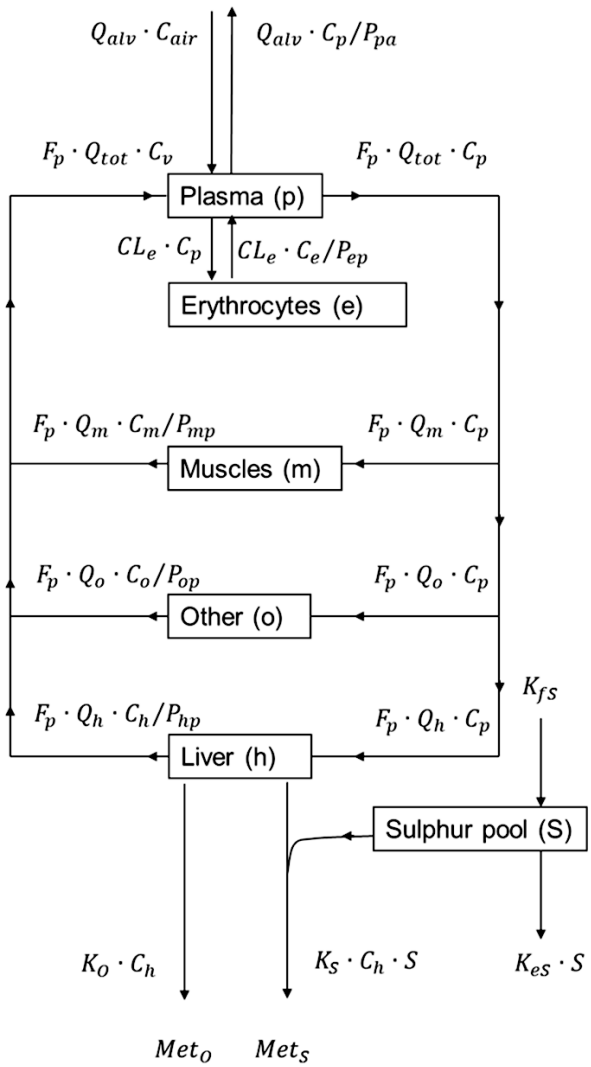

Figure 8.1 – Schematic description of the PBTK model for hydrogen cyanide. Symbols: Q – blood flows, C – cyanide concentrations, V – compartment volumes, P – partition coefficients, Fp – fraction of plasma to whole blood, S – amount of sulphur available for thiocyanate formation, K – metabolic rate constants, Met – metabolite formation rates.

Simulations of near-lethal exposure scenarios show that post-exposure breath levels of HCN during the first few minutes, after exposure, drops to about 0.2-1 ppm. These predicted breath levels are about two orders of magnitude higher than the background levels observed in non-exposed subjects.

The purpose of the model was to elucidate, through the use of a PBTK model, what concentration of HCN could be expected in exhaled breath after a near lethal exposure to HCN. These modelling efforts support the notion that HCN in breath may be used to identify cyanide poisoning. This PBTK model is, to our knowledge, the first of its kind estimating lethal HCN levels in exhaled air.

8.4 FORENSIC DATA – STUDY IV

In order to evaluate the contribution of HCN to fire-related fatalities data on COHb and blood cyanide from deceased fire victims in the period 1992-2009 were examined. The data was collected from two Swedish nationwide forensic databases (ToxBase and RättsBase). The databases contain data on COHb and/or cyanide in blood from 2303 fire victims, whereof 816 contained both COHb and cyanide information.

The statistical analyses showed that 4% of the victims had lethal or life-threatening blood cyanide levels (> 2 μg/g). 32 % had lethal COHb levels (>50% COHb). Nearly half of all fire victims (46%) had COHb levels at or above 30%. More than 30% had cyanide levels above 0.5 μg/g, an indication of significant HCN exposure. The cyanide levels may be underestimates, as cyanide is quickly eliminated in blood also after death.

Blood cyanide was positively correlated to COHb (Rho=0.5, $p<0.0001$). Blood cyanide was negatively correlated to age of victims but not to chronological order, whereas COHb was positively correlated to both age and chronology. No significant gender differences in blood cyanide or COHb levels were seen. Nonparametric statistical tests were used in the trend (Spearman) analyses and group comparisons (Mann-Whitney U and Kruskal-Wallis).

Our results support the notion that HCN may be a more important cause of death among fire victims than previously thought.

9 CONCLUSIONS AND DISCUSSION

We have seen that effects of cyanide on deceased fire victims are possibly more common than previously thought. In Study IV, nearly one third of the fire victims had blood cyanide levels above 0.5 μg/g, showing a considerable exposure to HCN. Furthermore nearly half of all fire victims (46%) had COHb levels at or above 30 %, where the combined exposure of HCN and CO might contribute to the lethal effect leading to the conclusion that treatment for cyanide poisoning is important in fire victims. At this point there is no available method for field measurements (Baud 2007).

We have suggested measurements in exhaled air as one way of diagnose of cyanide poisoning in fire victims. When measuring cyanide in exhaled air after exposure to fire gases it is important to establish whether the measurement reflects the systemic effects of the fire victim or if they represent the exposure levels in the fire. To answer this question the washout kinetic of hydrogen cyanide was studied in a controlled exposure to HCN. Extrapolating this low dose exposure to a high dose scenario gives that the washout from the high doses exposure is rapid and therefore measurement in exhaled air a few minutes after a high concentration exposure, for instance after exposure to fire gases, will represent the systemic effect. Hence, in theory measurement in breath has the potential as a diagnostic method.

To be able to distinguish between victims that suffer from cyanide poisoning and those how do not, expected breath levels in cyanide poisoning must be estimated. Also normal levels of healthy subjects are required. In Study II we measured background levels of HCN in exhaled breath. Together with other published data, background levels of cyanide in exhaled breath seem to be in the range of 0-62 ppb.

Since, cyanide does not follow Haber´s-law (see Equation 3.3.1) it is not possible to do simple extrapolations concerning breath levels of HCN corresponding those accepted after lethal or near-lethal exposures to HCN. To be able to draw conclusions on the expected breath levels after near-lethal exposures a PBTK model was developed in Study III. The result of this study shows that breath levels after near-lethal exposure can be expected to be about two orders of magnitude higher that the background levels in the studied populations.

9.1 CONCLUDING REMARKS

Many fires fatalities could be caused by cyanide poisoning or having cyanide poisoning as a contributing factor. Cyanide poisoning can be treated with antidotes. However, rapid initiation of the treatment is essential. Today, no good rapid diagnostic method is available.

We have investigated the possibility of using cyanide in breath as an indicator of cyanide poisoning. We have established that the washout of cyanide after a high concentration exposure is rapid. Therefore measurements in exhaled air a few minutes after exposure to cyanide will represent the systemic concentration of cyanide.

Our studies on background levels of cyanide in breath compared to expected levels in poisoned people shows that the difference could be sufficient to separate the two groups. Hence, measurement of exhaled air in fire victims can be used to indicate cyanide poisoning.

10 SVENSK SAMMANFATTNING

I Sverige dör årligen cirka 120 personer i bränder. Av dessa avlider de flesta till följd av exponering för giftiga brandgaser. De flesta av dessa dödsfall hänförs till kolmonoxid. Det finns dock flera andra giftiga gaser i brandrök. Exempelvis bildas vätecyanid när kväveinnehållande material såsom ull och polyuretanskum brinner.

Man kan tänka sig att många brandoffer dött till följd av cyanidförgiftning, alternativt efter en kombination av cyanid- och kolmonoxidförgiftning. Dock är det svårt att utvärdera cyanidens roll, bland annat eftersom cyanid fortsätter brytas ner i kroppen även efter att brandoffret avlidit.

Blodnivåer av karboxyhemoglobin och cyanid från avlidna brandoffer under perioden 1992-2009 samlades in från två svenska rättsmedicinska nationella databaser (ToxBase and RättsBase) (Studie IV). Analysen av dessa data stöder att vätecyanid bidrar mer än vad man tidigare trott till dödsfall i samband med bränder.

För behandling av cyanid finns det tillgängliga motgifter. Det är dock viktigt att behandlingen sätts in så fort som möjligt. Tyvärr finns det i dagsläget ingen bra och snabb diagnosmetod för cyanidförgiftning. Därför har vi undersökt möjligheten använda nivåer av cyanid i utandningsluft för diagnostiskt syfte.

I Studie I kunde ett kontrollerat försök med exponering för en låg koncentration vätecyanid visa att washout av cyanid i luftvägarna sker snabbt. Om detta resultat extrapoleras till en exponering för höga nivåer av cyanid, kan det ses att cyanidnivåerna i utandningsluft, ett par minuter det att exponeringen upphört representerar de systemiska nivåerna av cyanid i kroppen.

I Studie II mättes bakgrundsnivåerna av cyanid hos 40 frivilliga. De uppmätta nivåerna låg mellan <1.5-14 ppb. Tidigare publicerade data på normalbefolkningens cyanidnivåer ligger mellan 0 och 62 ppb. I Studie III konstruerades en fysiologiskt basserad toxikokinetisk modell med avsikt att uppskatta vilka nivåer som kan förväntas i utandningsluft efter exponering för dödliga eller nästan dödliga nivåer av cyanid. Modellen indikerade nivåer i området 0.2-1 ppm. En jämförelse mellan dessa resultat visar att den exponerade gruppen ligger mer än två gånger högre än den oexponerade gruppen. Detta indikerar att de båda grupperna borde kunna särskiljas genom att jämföra nivåerna av cyanid i utandningsluft.

Därav kan man dra slutsatsen att mätningar av cyanid i utandningsluft borde kunna användas för att indikera cyanidförgiftning.

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